RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 4/30/07 and 6/5/07, is acknowledged.

2. Claims 5-43 and 45-49 are pending.

3. Claims 7-30 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 5-6 and 31-43 and 45-49 are under examination as they read on a monoclonal antibody or antigen binding fragment thereof, a kit, a composition and a method of making.

5. Reference U listed on the PTO-892 was provided by applicant and reference V listed on the PTO-892 is used in applicat argument but was not provided.

6. Applicant's IDS, filed 4/30/07, is acknowledged.

7. In view of the amendment filed on 4/30/07 and 6/5/07, only the following rejections are remained.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 43 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that NSO cells are required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the cells may satisfy first paragraph. See 37 CFR 1.801-1.809 for the same reasons set forth in the previous Office Action mailed 11/29/06.

Applicant's arguments, filed 4/30/07 and 6/5/07, have been fully considered, but have not been found convincing.

The Declaration by Katarina Dahlenborg under 37 C.F.R. § 1.801-1.809 regarding deposit of the hybridoma that produces the mAb365 antibody at the Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, is sufficient to satisfy the deposit material for the hybridoma that produces the mAb365.

However, the issue of NSO cells has not been addressed by Application.

Further, amendment of the specification to disclose the date of deposit and the complete name and address of the depository is required as set forth in 37 C.F.R. 1.809(d).

10. Claims 33-37 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the a monoclonal antibody capable of binding to the extracellular I-domain of the integrin alpha10 chain which is specifically recognized by the monoclonal antibody produced by the hybridoma deposited under the accession number DSM ACC2583 or antigen-binding fragment thereof, a hybridoma cell line, a composition and a kit thereof does not reasonably provide **enablement** for an administration vehicle comprising the monoclonal antibody or fragment thereof claimed in claim 33 and 34 or a pharmaceutical composition for the treatment of musculoskeletal diseases, arthritis or atherosclerosis comprising a monoclonal antibody or a fragment thereof claimed in claim 35, or a pharmaceutical composition for gene therapy treatment of musculoskeletal diseases, arthritis or atherosclerosis comprising a monoclonal antibody or a fragment thereof claimed in claims 36 and 37, wherein the monoclonal antibody or fragment targets gene delivery to integrin alpha10beta1 expressing cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action mailed 11/29/06.

Applicant's arguments, filed 4/30/07 and 6/5/07, have been fully considered, but have not been found convincing.

Applicant argues under (a) *Alleged absence of a specific and detailed description of use* that the art at the time of filing described a large variety of antibodies against cell surface epitopes that have been successfully made and used in vivo in form of pharmaceutical compositions or administration vehicles. Most relevant, the art described a large variety of antibodies that had been developed as integrin antagonists and tested successfully in animal models or clinical trials. Shimaoka M, Springer TA., Therapeutic antagonists and conformational regulation of integrin function, Nat Rev Drug Discov. 2003 Sep;2(9):703- 16. These included monoclonal antibodies directed against the I-domain of integrin alpha chains. As a case in point, phase III clinical trials for treatment of psoriasis had been successfully concluded using a monoclonal antibody against the I-domain of integrin alphaL. Cather JC, Cather JC, Menter A., Modulating T cell responses for the treatment of psoriasis: a focus on efalizumab. Expert Opin Biol Ther. 2003 Apr;3(2):361-70.

As pointed by Applicant the prior art antibodies that show efficacy were against different molecule, i.e., the I-domain of alphaL integrin. However, the claims are drawn to a specific antibody against the I-domain of the alpha10 integrin subunit. Accordingly, the evidence applicant provided is not commensurate with the scope of the claimed monoclonal antibody that is capable of binding specifically to the extracellular I-domain of the integrin alpha10 chain.

Applicant argues under (b) *Alleged absence of workin.q examples providin,q evidence of reasonable expectation of effectiveness in vivo* that the fact that the specification does not contain a working example describing the use of a claimed pharmaceutical composition or administration vehicle in vivo does not by itself support a rejection based on non- enablement. "The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation." MPEP § 2164.02. In weighing the underlying factual findings in an enablement determination, the absence of a working example is not a strong factor if the art involved is predictable and well developed, as is the case here.

While the Examiner is well aware that the specification need not contain examples if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation, however, while the level of skill of in the art may be high, the state of the prior art is that it is in fact unknown and untested what are the underlying physiologic bases of the therapeutic effects of anti-I-domain alpha10 integrin subunit in the treatment of any disease including joint diseases, atherosclerosis or for gene delivery therapy. If the use disclosed is of such nature that the art is unaware of successful treatments with chemically analogous compounds, a more complete statement of how to use must be supplied "The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements...However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims." MPEP § 2164.03.

Applicant argues under (c) *Alleged lack of predictability in the art at the time the invention was made* that it was well established in the art at the time of filing that the I-domain is a major ligand- binding domain and that this domain recognizes the ligand directly. Shimaoka M, Springer TA., Therapeutic antagonists and conformational regulation of integrin function, Nat Rev Drug Discov. 2003 Sep;2(9):703-16. The art also recognized that because the I-domain binds the ligand directly, binding of another molecule, such as an inhibitory molecule, to the I-domain is "a straightforward way to block function [of the ligand-integrin interaction] competitively". Id. at 713 (emphasis and parenthesis added). Indeed, many of the inhibitory antibodies described in the art at that time were directed against the I-domain of integrins. For example, Diamond, M.S., et al,. The I domain is a major recognition site on the leukocyte integrin Mac-1 (CD11b/CD18) for four distinct adhesion ligands. J. Cell Biol. 120, 1031-1043 (1993); REF94. Applicant concludes that the art at the time of the invention was well developed and predictable, and there was a high degree of expectation of success in vivo for a pharmaceutical composition or administration vehicle comprising a monoclonal antibody that binds specifically to the I-domain of an integrin.

While the Examiner acknowledges that the I-domain is well known in the art at the time of the invention as a major ligand- binding domain and that this domain recognizes the ligand directly and that the ligands are bound by surface integrin receptors. However, the specialized medical

literature contains hundreds of reports indicating many integrin receptor/ligand interactions with different activities and different efficacy. The use of any anti-I-domain containing integrin has been proposed in several pathologic conditions, with different activities including anti-angiogenesis, anti-thrombotic and anti-metastatic action and now alpha10 as cell-surface marker for chondrogenic cells. It is unpredictable what activity or action the claimed antibody would have *in vivo*.

Applicant argues under (d) *Alleged absence of a rigorous correlation of pharmacological activity between the disclosed in vitro studies and an in vivo use* that the alleged absence of rigorous correlation of pharmacological activity between disclosed in vitro studies and an in vivo use relates to the absence of a working example and the predictability in the art, as discussed above. "An applicant need not have actually reduced the invention to practice prior to filing." MPEP § 2164.02. Hence, the absence of actual in vivo data is not a strong factor, let alone a sufficient basis in itself, for rejecting claims that pertain to an in vivo use, in particular where the art at the time of the invention was well developed and predictable, as is the case here.

It is the Examiner's position that the art is unpredictable with respect to the in vivo use of the claimed anti-I-domain of alpha10 integrin receptor (see above).

11. The following new ground of rejections are necessitated by the amendment submitted 4/30/07 and 6/5/07.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

35 U.S.C. § 102(e), as revised by the AIPA and H.R. 2215, applies to all qualifying references, except when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. For such patents, the prior art date is determined under 35 U.S.C. § 102(e) as it existed prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. § 102(e)).

13. Claims 42-43 and 45 are rejected under 35 U.S.C. 102(e) as being anticipated by US 20060123495 A1.

The `495 publication teaches a method for generating antibody-hybridomas reactive to alpha10beta1 (see published claims 48-50 in particular). The `495 publication teaches methods can be used for the production of monoclonal antibodies specific for alpha10 integrins using the alpha10 knockout mice [0304]. In one method, alpha10 knockout mice are immunized with

recombinant alpha10 or parts thereof, purified from an alpha10, or parts thereof, expressing cell lines. Two days after the last immunization, spleen cells from the mice are fused with NSO myeloma cells using polyethylene glycol. Fused cells are seeded in a 96-well microplate and grown in DMEM/F12 medium [0306]. Hybridoma cell clone supernatants (mAbs) are tested for anti-alpha10 antibody production by their ability to bind to immobilized alpha10 protein or parts thereof by e.g. ELISA and by binding to a cell line expressing alpha10beta1 in FACS analysis [0307]. Further the `495 publication teaches that the use of a non-human mammal and its progeny according to the invention is for the generation of wherein the antibodies are monoclonal antibodies (see ¶220 in particular). antibodies showing reactivity with alpha10-beta1, or a part thereof (see ¶218 in particular).

The reference teachings anticipate the claimed invention.

14. Claims 42 and 45-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 20060123495 A1 in view of Owens *et al* (of record).

The teachings of US 20060123495 A1 publication have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation that the antibody or fragment is humanized in claim 46, and that the fragments is selected form the group consisting of Fv, Fab, Fab`, F(ab`)2 and single chain antibodies in claim 47.

Owens *et al* teach the modification of murine antibodies such as a chimeric antibody, a single chain antibody, a Fab fragment, a $F(ab')_2$ fragment or a humanized antibody antibodies monoclonal antibody technology, chimeric, single chain, Fab fragments, and $F(ab')_2$. Owens *et al* further teach humanized antibodies use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely to induce an immune response. Also, antibody fragments are the reagents of choice for some clinical applications, and the chimeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement – dependent cytotoxcity (see the entire document).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody taught by the `495 publication as chimeric, humanized antibody, Fab and $F(ab')_2$ fragments taught by the Owens *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the humanized antibodies are much less likely to induce an immune response and because the antibody fragments are the reagents of choice for some clinical applications and the chimaeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement-dependent cytotoxcity as taught by Owens *et al*.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at

the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 42-43 and 45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 60-61 of copending Application No. 10/510,809. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are claiming a method of making a monoclonal antibody that binds to a protein which is specifically recognized by alpha10 or parts thereof using an alpha-10 knock-out mice. Since the `809 publication teaches an antibody to the whole molecule or parts thereof. The resultant antibody would bind to alpha10-I-doamin. The `809 application further teaches the use of NSO myeloma cell to fuse spleen cells from the mice [0306]. Hybridoma cell clone supernatants (mAbs) are tested for anti-alpha10 antibody production by their ability to bind to immobilized alpha10 protein or parts thereof [0307].

Claim 44 is included because antibody is antibody irrespective of how it is made. The patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985), MPEP 2113.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claim 42-43 and 45-47 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim60-61 of copending Application No. 10/510,809 in view of Owens *et al*.

The teachings of US `809 publication and Owens et al have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation that the antibody or fragment is humanized in claim 45, and that the fragments is selected form the group consisting of Fv, Fab, Fab`, F(ab`)2 and single chain antibodies in claim 47.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody taught by the `495 publication as chimeric, humanized antibody, Fab and $F(ab')_2$ fragments taught by the Owens *et al*. One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the humanized antibodies are much less likely to induce an immune response and because the antibody fragments are the reagents of choice for some clinical applications and the chimaeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement-dependent cytotoxcity as taught by Owens *et al*.

This is a provisional obviousness-type double patenting rejection.

18. Claims 5-6, 31-32, 38-41 and 48-49 are allowable.

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

February 25, 2008

/Maher M. Haddad/
Primary Examiner,
Art Unit 1644